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The prevalence of benign and malignant neoplasms in acromegalic patients

Występowanie łagodnych i złośliwych nowotworów u chorych na akromegalię

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Abstract

Introduction: In acromegalic patients, the prevalence of certain benign and malignant neoplasms is higher than that in the healthy population. We retrospectively evaluated the prevalence of tumours in acromegalic patients treated at our department: the regional centre for acromegalic patients for the Małopolskie voivodeship in Poland.

Material and methods: During the years 1983–2008, a hundred and one acromegalic patients (30 males and 71 women), of mean age 51.8 ± ± 15.4 years, were diagnosed and treated. Pituitary macroadenoma and microadenoma were stated in 63.4% and 25.7% of these patients, respectively. In 10.9% of these patients no data on tumour diameter were available. The mean observation period was 9.4 ± 6.5 years. The median levels of hGH and IGF-1 prior to neurosurgery were 20.2 (IQR = 34.9) ng/ml and 764.5 (IQR = 569.6) ng/ml, respectively.

Results: In the studied group of patients, we found the following prevalence of various tumours: nodular goitre — 64/101 patients (63.0%), polyps of the colon — 13/101 patients (13.0%); uterine polyps — 4/101 patients (4.0%); and prostate adenoma — 2/101 patients (2.0%). Among malignant tumours, thyroid cancer, endometrium and cervix cancer were the most frequent, each of these occurring in 3 patients (3.0%). Colon cancer prevalence was 2.0% (in 2 patients).

Conclusions: From our retrospective study, we suggest an overall increase of tumour incidence in acromegalic patients. Prospective multicentre studies are required to resolve the significance of this observation.

In our study group, the number of malignant neoplasms was significantly higher in patients with long-lasting uncontrolled disease (over 5 years), compared to patients with controlled disease. **(Pol J Endocrinol 2010; 61 (1): 29–34)**

Key words: *acromegaly, benign and malignant neoplasms, hGH and IGF-1*

Streszczenie

Wstęp: Pacjentów z akromegalią charakteryzuje częstsze niż w zdrowej populacji występowanie nowotworów zarówno łagodnych, jak i złośliwych. Autorzy ocenili retrospektywnie częstość występowania schorzeń nowotworowych u pacjentów z akromegalią leczonych w Klinice Endokrynologii w Krakowie, małopolskim ośrodku regionalnym leczenia akromegalii.

Materiał i metody: W latach 1983–2008 diagnozowano i leczono 101 pacjentów z akromegalią (30 mężczyzn i 71 kobiet), średnia wieku 51,8 ± 15,4 lat. U 63,4% chorych stwierdzono obecność makrogruczolaka w przysadce, u 25,7% mikrogruczolaka, a u 10,9% chorych brak danych określających wielkość guza. Mediana stężenia hGH i IGF-1 przed operacją wynosiła odpowiednio: 20,2 (IQR = 34,9) ng/ml i 764,5 (IQR = 569,6) ng/ml.

Wyniki: W analizowanej grupie chorych stwierdzono występowanie: wola guzowatego — u 64/101 pacjentów (63%), polipy jelita grubego — u 13/101 pacjentów (13%), polipy macicy — u 4/101 pacjentów (4%), gruczolaka prostaty — u 2/101 pacjentów (2%). Spośród nowotworów złośliwych najczęściej występowały: rak tarczycy, rak *endometrium* i szyjki macicy, każdy u 3 chorych (3%). Raka jelita grubego stwierdzono u 2 pacjentów (2%).

Wnioski: Na podstawie przeprowadzonego badania retrospektywnego autorzy sugerują częstsze występowanie guzów nowotworowych u pacjentów z akromegalią. Potrzebne są badania prospektywne większych liczebnie grup pacjentów, żeby określić znaczenie tych obserwacji.

W badanej grupie pacjentów nowotwory złośliwe występowały znamiennie częściej u pacjentów z długotrwałą niekontrolowaną akromegalią (> 5 lat), w porównaniu z osobami, u których kontrolowano przebieg choroby. **(Endokrynol Pol 2010; 61 (1): 29–34)**

Słowa kluczowe: *akromegalia, łagodne i złośliwe nowotwory, hGH i IGF-1*

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Introduction

Acromegaly is a rare chronic disease caused by increased secretion of growth hormone (hGH). Over 99% of cases of acromegaly result from the presence of pituitary adenoma developed from somatotrope cells which normally produce GH in the pituitary. The estimated prevalence of acromegaly ranges between 50–70 cases/ /million.

A number of studies have confirmed increased morbidity and mortality in acromegalic patients, related mainly to cardiovascular, cerebrovascular, respiratory, and metabolic disease complications [1]. Acromegalic patients are also believed to show a risk higher than in the general population of developing benign and malignant tumours mainly of the digestive tract (particularly colorectal), brain, breast, or thyroid gland, as suggested by several multicenter studies [2, 3].

The aim of this preliminary study was to perform a single-centre evaluation of the prevalence of benign and malignant neoplasms in a group of acromegalic patients. The Department of Endocrinology at UJCM is a regional centre for acromegalic patients for the Małopolskie voivodeship in Poland. Our acromegaly group consisted of 101 patients in whom we determined the number of tumours and their localization. We also assessed the relationship between the presence of malignant tumours and serum levels of hGH and insulin-like growth factor 1 (IGF-1) and the duration of controlled and uncontrolled disease.

Material and methods

A group of 101 acromegalic patients (30 males, 71 women), mean age 51.8 ± 15.4 years, were diagnosed and treated in our department during the years 1983–2008. Pituitary macroadenoma and microadenoma were stated in 63.4% and 25.7% of these patients, respectively. In 10.9% of these patients no data on tumour diameter were available (Fig. 1). The mean observation period was 9.4 ± 6.5 years. The mean period of uncontrolled disease and the mean quiescent period were 6.4 ± 5.2 and 3.0 ± 5.5 years, respectively. The serum concentrations of hGH and IGF-1 were measured using IRMA (DiaSorin) and RIA (Biosource) methods, respectively. In our analysis, we scored neoplasms only in patients for whom acromegaly was stated as their primary diagnosis. Our study was based on retrospective analysis of patient histories.

For statistical analysis the basic statistics, Shapiro-Wilk, U Mann-Whitney, Wilcoxon, and Fisher tests, were used.

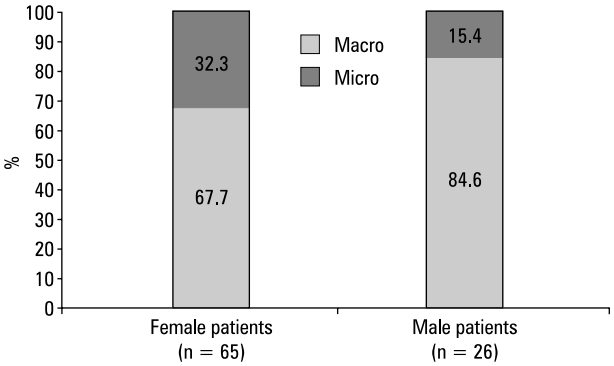

Figure 1. *Type of pituitary adenoma in acromegalic patients, depending on their sex (%), n = 91. In 10 patients, no data on tumour size were available*

Rycina 1. *Typ gruczolaka przysadki u pacjentów z akromegalią w zależności od płci (%), n = 91. U 10 pacjentów brak danych dotyczących wielkości gruczolaka*

Results

In acromegalic male patients a higher frequency of macroadenoma (84.6%) was observed, as compared to female patients (67.7%). Different age-related frequencies of acromegaly were observed in the groups of women and men. As shown in Figure 2, acromegaly was most frequent in women aged between 50 and 59 years (in their 6th decade) and in men aged between 40 and 49 years (in their 5th decade). The median levels of hGH and IGF-1 prior to treatment were 20.2 (IQR = 34.9) ng/ml and 764.5 (IQR = 569.6) ng/ml, respectively, as compared to median levels of hGH and IGF-1 at the time of completion of this study, for all patients in the group: 2.1 (IQR = 4,0) ng/ml and 304.3 (IQR = 397.3) ng/ml, respectively (Fig. 3), the differences being statistically significant ($p < 0.05$).

At the time of completion of this study, only the median concentration of IGF-1 (Fig. 3) was significantly higher in patients with active acromegaly 535.6 (IQR = = 505.0) ng/ml, as compared to patients in whom the disease was controlled, 172.9 (IQR = 115.7) ng/ml ($p< 0.05$).

The prevalence of various tumours in patients in the studied group was as follows: nodular goitre — 63.0% (64 patients), polyps of the colon — 13.0% (13 patients); uterine myoma and polyps — 12% (12 patients) and 4.0% (4 patients), respectively, and prostate adenoma — 2% (2 patients). Meningioma occurred in 3 (3.0%), adrenal adenoma in 2 (2.0%) and parathyroid adenoma in 1 (1.0%) of the patients studied. Among malignant tumours, thyroid cancer, endometrium and cervix cancer were the most frequent, each of these occurring in 3 (3.0%) of the patients. Colon cancer occurred in 2 (2.0%)

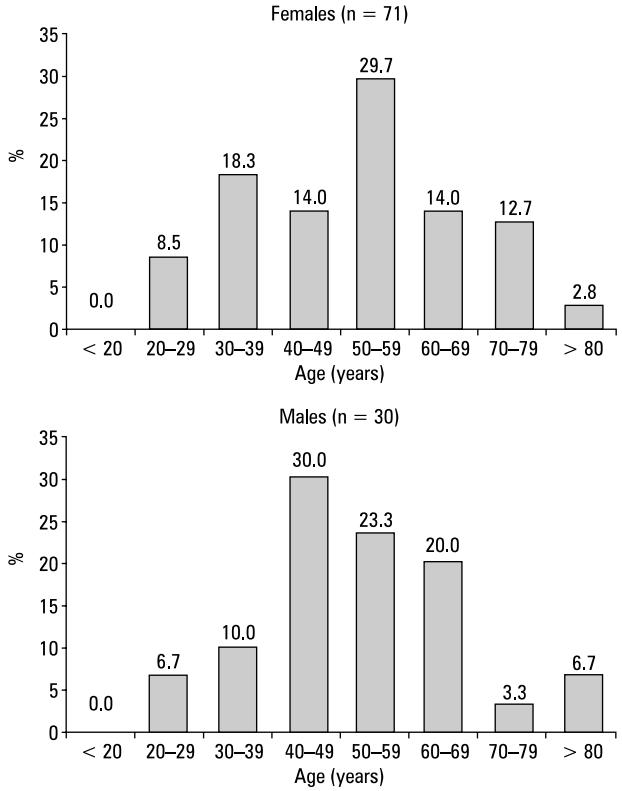

Figure 2. *Frequency of acromegaly in patients in the female and male age groups (%), n = 101*

Rycina 2. *Częstość występowania akromegalii u kobiet i mężczyzn w zależności od wieku (%), n = 101*

of the patients. Single cases of breast, stomach, skin, and small-cell lung cancer, were also observed (Table I). The level of PSA was measured in all 30 men under observation: the mean concentration was 1.3 ± 1.6 ng/ml.

Figure 4 represents the number of malignant and benign neoplasms *versus* time of total duration of the disease and time of uncontrolled acromegaly. The dependence of the number of malignant neoplasms on the duration of uncontrolled disease: less than 5 years and over 5 years, was found to be statistically significant ($p \leq 0.05$, Fisher test). In our group of studied patients we found no dependence between the concentrations of hGH and IGF-1 and the frequency of occurrence of malignant neoplasms.

Discussion

Retrospective studies on mortality in acromegaly patients have shown some 24% of cancer-related deaths in a group of over 5000 acromegalic patients [4]. This has been recognized only recently, as improved management of this disease has allowed acromegalic patients to survive long enough to reach the age of increased cancer risk. The aetiology of these tumours is unknown, but it probably reflects increased levels of hGH and insulin-like growth hormone (IGF-1) in the blood. Another hypothesis is that due to possible genetic and epigenetic alterations, acromegaly is predisposed to increased cancer risk [4].

The prevalence/incidence of cancer in patients with acromegaly remains controversial, as no increase in the risk of cancer in acromegaly has been stated by some authors [1, 5]. On the other hand, increased relative risk (1.5–4-fold) for acromegalic patients to develop tumours, including colon, thyroid gland, prostate, brain, lung, kidney, and skin cancers, and possibly haematological malignancies, has also been reported [4]. In Sweden and

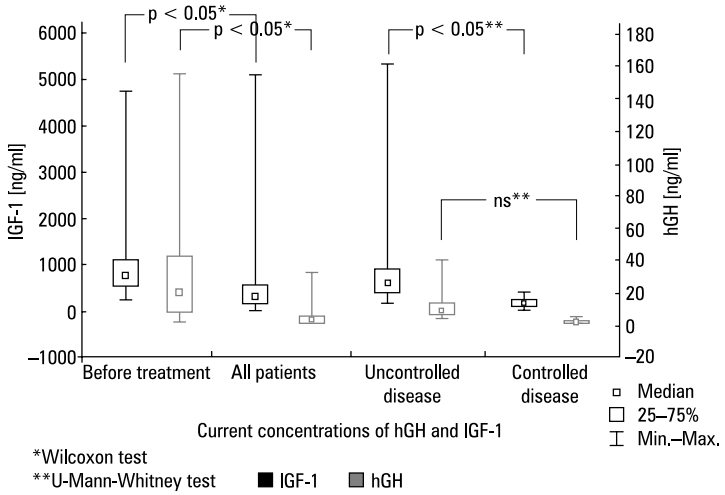

Figure 3. *Median values of hGH and IGF-1 before treatment, and at completion of this study. The differences between median levels of hGH and IGF-1 prior to treatment and at completion of this work are statistically significant (p < 0.05)*

Rycina 3. *Wartości median stężenia hGH i IGF-1 przed leczeniem i na zakończenie niniejszej pracy. Różnice wartości mediany stężenia hGH i IGF-1 przed leczeniem i na zakończenie niniejszej pracy są znamienne statystycznie (p < 0,05)*

Table I. *Number of malignant and benign neoplasms in acromegalic patients, n = 101*

Tabela I. *Liczba złośliwych i łagodnych nowotworów u pacjentów z akromegalią, n = 101*

Localization	Malignant neoplasm	Benign neoplasm	Total
Thyroid gland	3	64	67
Colon	2	13	15
Stomach	1	1	2
Lung	1	–	1
Skin	1	1	2
Uterus	3	16	19
Breast	1	–	1
Liver	–	3	3
Nasopharynx	–	1	1
Meningioma	–	3	3
Adrenal glands	–	2	2
Parathyroid glands	–	1	1
Prostate	–	2	2
Bone	–	1	1
Total	12	108	120

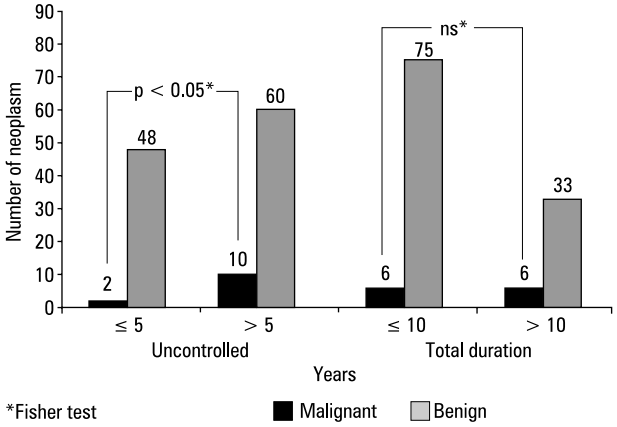

Figure 4. *Number of malignant and benign neoplasms versus total duration of disease and duration of uncontrolled acromegaly. The number of malignant neoplasms in the group of patients with uncontrolled disease over 5 years is significantly higher than that in the group of patients with uncontrolled disease less than 5 years (Fisher test, p ≤ 0.05)*

Rycina 4. *Liczba nowotworów łagodnych i złośliwych w zależności od całkowitego czasu trwania akromegalii i czasu trwania choroby aktywnej. Liczba nowotworów złośliwych w grupie pacjentów z aktywną akromegalią powyżej 5 lat jest znamiennie wyższa w porównaniu do grupy pacjentów z aktywną chorobą trwającą poniżej 5 lat (test Fishera, p ≤ 0,05)*

Denmark, an increased risk SIR (standardized incidence ratio) of 1.5 for all cancers, except prostate, was found in acromegaly, as compared to population values [2]. In our retrospectively analysed group of acromegaly patients we observed 12 malignant tumours, which gives a prevalence of 12% (12/101 patients), compared to the crude incidence rate of 666 new cancer cases/100 000 inhabitants (0.67%) in the Małopolska region in 2006 [6]. Additionally, 108 benign tumours, mainly of the thyroid, colon, and uterus, were found (Table I).

In acromegalic patients, the reported frequencies of diffuse goitre and nodular goitre were 78-92% and 63%, respectively [7, 8]. We also found nodular goitre by USG in 64/101 (63%) of our patients, confirming these reports. However, we did not observe any positive relationship between GH/IGF-1 concentration and thyroid volume, as found by Hermann et al. [8]. The prevalence of thyroid cancer in acromegaly is not known, as the populations of acromegalic patients studied are too small. In retrospective studies, thyroid cancer constitutes 3.1% of all malignancies in acromegaly. The evaluated relative risk for thyroid cancer was 2.5–4.3, but the number of patients with thyroid cancer was very low: 1–3 patients [4]. Tita et al. [7] estimated the prevalence of thyroid cancer at 5.6% (7/125) in acromegalic patients, as compared to 0.1% in the general population over iodine deficient areas. In an Italian multi-centre study, a thyroid cancer prevalence of 1.2% (3/258 patients) was found by Gasperi et al. [9].

In our material the prevalence of thyroid cancer was 3% (3/101 patients), in two of whom follicular cancers and one papillary were stated. The cancer register at the Centre of Oncology in Kraków [6] quotes the crude incidence rate of thyroid cancer in the Małopolska region in 2006 at 10.8 for females and 2.2 for males per 100,000 inhabitants. We can therefore state an increase in the prevalence of thyroid cancer in acromegaly; however, the small size of our patient group does not enable standard epidemiological tools to be applied.

In vitro studies confirm the presence of IGF-1-R on thyroid cancer cells and synthesis of IGF-1 by follicular cells and papillary cell lines, while surgical thyroid specimens suggest local autocrine loop [4], thus supporting the hypothesis of the role of IGF-1 in the control of thyroid follicular cell proliferation. Based on our experience, we believe that due to its high prevalence, nodular goitre in acromegaly should be monitored according to ATA guidelines, and FNAB (Fine Needle Aspiration Biopsy) should be performed in nodules of diameter ≥ 1 cm [10].

The issue of colon cancer risk in acromegaly is also controversial [11]. As colon cancer may result from colon polyp degeneration, the prevalence of colon polyps in patients with acromegaly has been the subject of

many studies. A 22–26% prevalence of colon adenoma was demonstrated in a prospective study at Bartholomew's Hospital, UK [12] and by a multicenter study in Italy [13]. In our group of patients, we found the prevalence of colon polyps to be 13% (13/101). Prospective studies show that up to 45% of these patients have colonic polyps, which are adenomatous in 24% of cases [14]. The correlation between hGH and IGF-1 concentrations and the incidence of colonic polyps has not been clearly elucidated. In our study group, we also found no relationship between hGH and IGF-1 concentration and the frequency of occurrence of malignant neoplasms.

The prevalence of colon carcinoma in acromegaly was evaluated at 4–5% [12, 13]. We observed only two cases of colon cancer (2%) which might be a biased value due to the small group of our patients. For comparison, the crude incidence rate of colorectal cancer in the Małopolska region in 2006 was estimated at 40.0 for males and 30.6 for females per 100,000 inhabitants [6]. Based on three population studies in acromegalic series, Renehan [15] calculated the risk ratio for colorectal cancer to be 2.04. Until recently, total colonoscopy was advised for newly diagnosed patients [4] and then according to American Cancer Society guidelines [16] for patients with increased risk, every 5 years if no cancer or polyps were detected. This statement is currently under revision as, based on a population study and the definition of the high-risk group of colorectal cancer, acromegalic patients are just above the average-risk value. Therefore, Renehan recommends screening colonoscopy after the 50th birthday of acromegalic patients (15).

A 4-fold higher risk of breast cancer in acromegalic patients stated by Nabarro [17] has not been confirmed by other authors. In our group of 101 patients, we found only one case of breast cancer.

Acromegaly is associated with prostate hyperplasia and macro- and microcalcifications, but the incidence of cancer does not appear to be elevated significantly [18]. In our study group, the PSA level was measured in all 30 men under observation, their mean PSA concentration falling within normal range. Prostate adenoma, but no cancer, was stated in 2 patients.

Ron, Orme and Barris [1–3] did not confirm any increased prevalence of lung cancer in acromegalic patients, although SCLC (small cell lung cancer) and non SCLC express IGF-1R (IGF-1 receptor) and produce IGF-1, and stimulation with exogenous IGF-1 induces proliferation of small cell lung cancer cell lines [19, 20]. In our group of patients, one case of SCLC (1%) was found, as compared with the crude incidence rate of all lung cancer of 80.8 for males and 22.0 for females per 100,000 inhabitants of the Małopolska region in 2006 [6].

We found that the dependence of the number of malignant neoplasms on the duration of uncontrolled disease, less than 5 years and over 5 years, was statistically significant. The difference in the number of malignant neoplasms versus total duration of acromegaly (less than 10 years and over 10 years) was not significant. In a nationwide survey for cancer incidence in acromegaly in Finland [21], three cases of colorectal cancer *v.* 0.7 expected were found after 5 years of observation in the group of patients with post-treatment hGH concentration ≥ 2.5 ng/ml. This proves the importance of efficient treatment of acromegaly not only to reduce mortality but also to reduce the risk of cancer occurrence. Acromegaly is a rare disease indeed, making it difficult for individual centres to gather sufficient numbers of patients for statistical analysis. Therefore, due to the small population of our study group (101 patients) and the small numbers of cases of malignant neoplasms found [7], we report our results in terms of prevalence within our group, rather than as standardized incidence rates, SIR. Meta-analyses and multicentre studies have to be undertaken to estimate the risk of cancer in acromegaly patients.

Conclusions

Based on our retrospective study, we suggest an overall increase of tumour incidence in acromegalic patients. Prospective studies are required to resolve the significance of this observation.

In our group of patients, we found the number of malignant neoplasms to be significantly higher in patients with long-lasting uncontrolled disease (over 5 years). We found no statistically significant difference in the number of malignant neoplasms versus total duration of acromegaly (less than 10 years and over 10 years).

We propose that, due to the high incidence of nodular goitre, acromegalic patients should be monitored according to ATA guidelines. In particular, fine-needle aspiration biopsy of nodules of size greater than 1 cm should be performed.

We consider that regular screening of acromegalic patients for polyps and colon cancer after their 50th birthday, and for prostate cancer (PSA, rectal examination or USG), is advisable.

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